

Amendments to the Specification:

Please change the title at page 1, line 1, as follows.

INTEGRIN/ADHESION ANTAGONISTS

Please replace the paragraph beginning at page 5, line 23 through page 6, line 2, with the following:

C₁ Of particular interest here is use of peptide libraries and other techniques in the discovery of peptides that inhibit integrins, selectins, cellular adhesion molecules, or their respective receptors. A number of such peptides identified in the art are summarized in Table 2. For randomly generated peptides, peptide libraries typically were screened for binding to a receptor for an integrin ligand (e.g., $\alpha 4\beta 1$). For purposes of this application, these molecules are collectively termed, "Integrin/adhesion antagonists."

Replace page 6, line 10, with the following:

C₂ **Table 2— Integrin/adhesion antagonist peptides**

Replace the paragraphs beginning at page 7, line 14 through page 8, line 6, with the following:

The present invention concerns therapeutic agents that have integrin antagonist activity, including activity of known peptides but with better pharmaceutical characteristics (e.g., half-life). In accordance with the present invention, such compounds comprise:

- C₃
- a. an integrin/adhesion antagonist peptide; and
 - b. a vehicle, such as a polymer (e.g., PEG or dextran) or an Fc domain, which is preferred; wherein the vehicle is covalently attached to the integrin/adhesion antagonist. The vehicle and the integrin/adhesion antagonist may be linked through the N- or C-terminus of the integrin/adhesion antagonist, as described further below. The preferred vehicle is an Fc domain, and the preferred Fc domain is an IgG Fc domain. integrin/adhesion antagonists can be generated by phage display, RNA-peptide screening and the other techniques mentioned herein.

The present invention also concerns a process by which the in vivo half-life of one or more biologically active peptides is increased by fusion with a vehicle. In this invention, pharmacologically active compounds are prepared by a process comprising:

- a. selecting at least one integrin/adhesion antagonist peptide; and

CF b. preparing a pharmacologic agent comprising at least one vehicle covalently linked to at least one amino acid sequence of the selected peptide.

Replace the paragraph beginning at page 14, lines 19-28, with the following:

CF The term "integrin/adhesion antagonist" comprises peptides that inhibit or down-regulate the activity of integrins, selectins, cell adhesion molecules, integrin receptors, selectin receptors, or cell adhesion molecule receptors. Exemplary integrin/adhesion antagonists comprise laminin, echistatin, the peptides described in SEQ ID NOS: 7 to 21 hereinafter, the peptides in Tables 3, 4, and 5 hereinafter, and those described in the references in Table 2. Those of ordinary skill in the art appreciate that each of these references enables one to select different peptides than actually disclosed herein by following the disclosed procedures with different peptide libraries.

CF Replace the paragraph beginning at page 15, line 18, with the following:

P¹, P², P³, and P⁴ are each independently sequences of integrin/adhesion antagonist peptides;

CF Replace the paragraph beginning at page 16, line 11, with the following:

CF Peptides. Any number of integrin/adhesion antagonist peptides may be used in conjunction with the present invention. Targeting peptides are also of interest, including tumor-homing peptides, cell-type specific peptides and the like. All of these classes of peptides may be discovered by methods described in the references cited in this specification and other references.

Please change the paragraph at page 17, lines 5-32, with the following:

Peptides particularly of interest for use in the present invention include laminin, which has the sequence

YIGSR

(SEQ ID NO: 7)

CF echistatin, which has the sequence

ECESGPCCRNCKFLKEGTICKRARGDDMDDYCNGKTCDCPRNPHKGPAT

(SEQ ID NO: 8)

RGD, NGR and derivatives thereof having the sequences

RX₁ETX₂WX₃

(SEQ ID NO: 9)

wherein X_1 , X_2 , and X_3 are any amino acid;

$RX_1ETX_2WX_3$

(SEQ ID NO: 10)

$CX_1X_2RLDX_3X_4C$

(SEQ ID NO: 11)

wherein X_1 , X_2 , X_3 and X_4 are any amino acid;

$CXXRGDC$

(SEQ ID NO: 12)

$X_1X_2X_3RGDX_4X_5X_6$

(SEQ ID NO: 13)

wherein X_1 , X_3 , X_4 , and X_6 are capable of forming a bridge (by disulfide bonds, peptide bonds or lactam bonds)
and X_2 and X_5 are 1 to 5 amino acids;

$CX_2CRGDCX_5C$

(SEQ ID NO: 14)

wherein X_2 and X_5 are 1 to 5 amino acids;

$X_1X_2DDX_4X_5X_7X_8$

(SEQ ID NO: 15)

wherein X_1 and X_6 each is an independently selected amino acid, X_2 and X_7 together equal 0 to 4 amino acids,
each amino acid of which is independently selected, X_4 is selected from the group consisting of glycine and
leucine, and X_5 is selected from the group consisting of tryptophan and leucine;

$X_1X_2X_3DDX_4X_5X_6X_7X_8$

(SEQ ID NO: 16)

wherein X_1 and X_6 each is an independently selected amino acid, X_2 and X_7 together equal 0 to 3 amino acids,
each amino acid of which is independently selected, X_3 is selected from the group consisting of tryptophan and
proline, X_4 is selected from the group consisting of glycine and leucine, X_5 is selected from the group consisting
of tryptophan and leucine, and X_6 is selected from the group consisting of leucine, tryptophan, and methionine.
in which the The substituents X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , and X_8 are as defined in International applications WO
95/14714, published June 1, 1995 and WO 97/08203, published March 6, 1997 (corresponding to U.S. Pat.
Nos. 5,627,263 and 5,817,750, respectively), which are incorporated by reference in their entirety.

Appl. No. 09/840,277
Amdt. dated July 18, 2003
Reply to Office Action of Feb. 26, 2003

Replace the line 1 at page 62, with the following:

~~Integrin~~/Adhesion Antagonists